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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/812,238

Filing Date: March 29, 2004

Appellant(s): WARY ET AL.

Benjamin Aaron Adler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/12/08 appealing from the Office action mailed 10/10/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,808,819	CHENG	9-1998
5,567,440	HUBBELL	10-1996

Vassilev *et al.* "Inhibition of cell adhesion by antibodies to Arg-Gly-Asp (RGD) in normal immunoglobulin for therapeutic use (intravenous immunoglobulin, IVIg)" Blood. vol. 93, no.11(Jun 1, 1999), pp. 3624-3631.

Bendayan M., "Possibilities of false immunocytochemical results generated by the use of monoclonal antibodies: the example of the anti-proinsulin antibody" J. Histochem. Cytochem. Vol. 43, 1995, pp. 881-886.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Vassilev *et al* (Blood. 1999 Jun 1;93(11):3624-31), as is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886).

Vassilev *et al* teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes (see page 3629, bridging ¶ and page 3624, 2nd col., 1st full ¶ in particular). Vassilev *et al* teach that IVIg contains antibodies to Arg-Gly-Asp (RGD) sequence, and the attachment site of a number of adhesive extracellular matrix proteins, including ligands for $\beta 1$, $\beta 3$ and $\beta 5$ integrins (see abstract). Vassilev *et al* teach a method of inhibiting integrin-dependent platelet aggregation (cell-cell) to fibronectin (Fn) (ligand) "integrin ligand-mediated cell-cell interaction" by anti-RGD antibodies (see page 3626, 1st col., 2nd paragraph and Fig. 4 in particular). Further, adhesion of thrombin-stimulated platelets to von Willebrand factor or Fg (integrin ligand-mediated cell-cell interaction) was

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completely inhibited by affinity-purified anti-RGD antibodies. Vassilev *et al* teach that the presence of natural IgG antibodies to the RGD motif may contribute to the immunomodulatory and anti-inflammatory effects of the therapeutic preparations of normal IgG (see abstract).

Vassilev *et al* teach that affinity purified anti-RGD antibodies block the adhesion of Raji cells to Fn. By inhibiting leukocyte adhesion, antibodies in IVIg that recognize the RGD adhesion motif may contribute to the anti-inflammatory effects of IVIg (see page 3629, top ¶). The reference teaches that the inhibition of cell adhesion by anti-RGD antibodies can be critical in the Fn matrix formation involving $\alpha 5/\beta 1$ integrins and the subsequent cell adhesion in the progression of metastasis (see page 3629, 2nd co., 1st full ¶). Further, Vassilev *et al* teach that the MoAbs to integrins and adhesion-blocking peptides have been used in experimental models of autoimmune and inflammatory disease as well as the treatment of patients with solid organ allograft rejection (see page 3629, 2nd col. 2nd ¶ in particular).

Vassilev *et al* reference teaches that the anti-RGD antibodies bind to peptide and proteins expressing the RGD sequence (see page 3625, 1st col., under Binding assays). Vassilev reference teaches that the ability of the RGD fraction of IVIg bound to fibronectin, fibrinogen, vitronectin, VWF and laminin in a dose dependent manner (see Fig. 1 and page 3626, col., 1, top ¶). Given that the claimed SEQ ID NO: 2 and 41 are RGD-containing peptide sequences, the referenced anti-RGD antibodies would bind to the claimed SEQ ID NO: 2 (EGYIQNYRCRGDDSKVQEAR) and 41 (CRGDD).

Moreover, antibodies “cross-react” with antigens with homologous amino acid residues. The reference anti-RGD antibody would bind to the peptide comprises SEQ ID NO: 41 (CRGDD) and 2 (EGYIQNYRCRGDDSKVQEAR) due to the shared sequence homology (RGD motif). As is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that “an antibody directed against such a sequence, although

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still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

While the prior art teachings may be silent as to the "antibody blocks binding of $\alpha\beta\beta 3$ and/or $\alpha\beta\beta 1$ integrins to the cell surface VCIP" per se; the method and the product used in the reference method are the same as the claimed method. Therefore "antibody blocks binding of $\alpha\beta\beta 3$ and/or $\alpha\beta\beta 1$ integrins to the cell surface VCIP" is considered inherent properties. The anti-RGD antibodies administered bind to a ligand comprising the RGD motif due to properties inherently possessed by the antibody. That is the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious.

Since the office does not have a laboratory to test the reference antibodies, it is Appellants' burden to show that the reference antibody does not bind to the SEQ ID NO:2 and 41 recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,807,819 in view of U.S. Pat. No. 5,567,440 and Vassilev *et al* as is evidenced by Bendayan (*J. Histochem. Cytochem.* 1995, 43:881-886).

The '819 patent teaches a method of treating angiogenesis comprising administering to the subject RGD-containing peptides (agents) (see abstract and the entire document). The '819 patent further teaches that angiogenesis is required for the growth of solid tumors and neovascularization serves as a conduit for metastasis (see col. 9, lines 19-21 in particular). Further, the '819 patent teaches methods of using the Arg-Gly-Asp containing peptides such as CRGDDVC (patented SEQ ID NO: 17) to alter $\alpha\text{v}\beta 3$ integrin receptor-mediated binding of a cell endothelial cell to a matrix. The '819 patent teaches further teaches methods for ameliorating the severity of a pathology characterized by an undesirable level of angiogenesis in a subject using RGD-containing peptides (see the entire document including the abstract).

The claimed invention differs from the '819 patent teachings only by the recitation of antibody to SEQ ID NO: 2 or 41 in claims 15 and 32.

The '440 patent teaches that cell adhesion plays an important role in human disease. These interactions proceed by the interaction of receptors upon the surface of a cell with proteins or glycosaminoglycans upon the surface of another cell or within the extracellular matrix. The '440 patent further teaches that routes to the interruption of these interactions typically involve competitive inhibition of these receptor-ligand interactions, for example, with antibodies, soluble ligands which act as receptor antagonists (e.g., cyclic RGD peptides), soluble receptors, or other competitors (see col., 1 lines 17-30 in particular).

Vassilev *et al* teach a method of inhibiting integrin-dependent platelet aggregation “cell-cell interaction” to Fn (integrin ligand-mediated cell-cell interaction) by anti-RGD antibodies (see page 3626, 1st col., 2nd paragraph and Fig. 4 in particular). Vassilev *et al* further teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes. For instance, cyclic RGD peptides have been shown to inhibit $\alpha 4\beta 1$ -dependent adhesion of T cells to cytokine-activated endothelial cells (see page 3629, 1st col., last paragraph to the 2nd col., 1st paragraph in particular). Further, antibodies “cross-react” with antigens with homologous amino acid residues. The reference anti-RGD antibody would bind to

the peptide comprises SEQ ID NO: 41 and 2 due to the shared sequence homology. As is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that “an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen” (page 886, last paragraph in particular).

The limitation “blocks the binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins to cell surface VCIP” would be expected properties of the resultant method.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CRGDDVC cyclic peptide taught by the '819 patent with anti-RGD antibody taught by Vassilev *et al* in a method of inhibiting angiogenesis in a subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because routes to the interruption of cell-cell interactions typically involve competitive inhibition of these receptor-ligand interactions with either receptor antagonists (e.g., cyclic RGD peptides), antibodies or other competitors as taught by the '440 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Rejection of Claims 8 and 14-15 under 35 U.S.C. §102(b) over Vassilev *et al.*, as is evidenced by Bendayan

At the bottom of page 10 of the brief, Appellants submit that Vassilev *et al.* do not teach a method of inhibiting $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin ligand-mediated cell-cell interaction, as recited in Applicants' claim 8. Vassilev *et al.* do not teach a method of inhibiting tumor growth, inflammation and/or angiogenesis in a patient, as recited in Applicants' claim 15. Applicants demonstrate that Appellants' antibody blocks the interaction between VCIP and the $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins (pg. 35-36, Example 16; Fig. g). Also, Appellants teach that $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin ligand-mediated cell-cell interaction have clear pathological consequences, such as inflammation and tumor-induced angiogenesis (page 19, II. 18-24). In addition, Appellants demonstrate in an *in vivo* mouse model of human colon cancer that VCIP is expressed in tumor vasculatures near $\alpha v\beta 3$, potentiates tumor growth and regulates tumor angiogenesis by recruiting endothelial cells (page 48, Example 27; Figures 20A-20). This is not found to be persuasive. Vassilev *et al* teach the ability of the anti-RGD antibodies in IVIg to inhibit integrin-dependent platelet aggregation to fibronectin (Fn) (integrin ligand-mediated cell-cell interaction) (see Fig. 4, page 3627). Vassilev *et al* teach that RGD motif has a central role in mediating cell-to-cell and cell-matrix adhesion in a variety of immunological and inflammatory processes (see page 3629, bridging ¶¶). Vassilev *et al* teach that the inhibition of cell adhesion by antibodies to Arg-Gly-Asp (RGD) in normal immunoglobulin-for therapeutic use. Specifically, Vassilev *et al* teach IVIg contains antibodies to the Arg-Gly-Asp (RGD) sequence, and the attachment site of a number of adhesive extracellular matrix proteins, including ligands for $\beta 1$, $\beta 3$ and $\beta 5$ integrins. Anti-RGD F(ab')₂ antibodies inhibited the adhesion of activated $\alpha 4\beta 1$ integrin-expressing B cells to Fn. Further, adhesion of thrombin-stimulated platelets to von Willebrand factor or Fg (integrin ligand-mediated cell-cell interaction) was completely inhibited by affinity-purified anti-RGD antibodies. Vassilev *et al* teach that the presence of natural IgG antibodies to the RGD motif may contribute to the immunomodulatory and anti-inflammatory effects of the therapeutic preparations of normal IgG (see abstract). Regarding tumor growth, claim 15 recites the

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conditions "tumor growth, inflammation and/or angiogenesis" in the alternative. In this case, there is no requirement for the prior art to meet all the claimed conditions. Yet, Vassilev teach that integrins play a critical role in inflammation, immune responses, thrombosis, malignant transformation, and metastasis (see page 3624, 2nd col., 1st ¶). Metastasis formation was shown to be suppressed by agents interfering with RGD-dependent adhesion in several animal models and *in vitro* models by using human tumoral cells. MoAbs to integrins and adhesion-blocking peptides have been used in experimental models of autoimmune and inflammatory diseases as well as in the treatment of patients with solid organ allograft rejection. Because human IgG autoantibodies recognizing the same target molecules as these MoAbs are present in IVIg, we speculate that IVIg may have similar *in vivo* effects (see p. 3629, 1st full ¶).

At the middle of page 11 of the brief, Appellants argue that in distinct contrast, Vassilev *et al.* teach a method of inhibiting adenosine diphosphate-induced platelet aggregation (pg. 3624, 2nd col., 2nd full PP) by naturally produced antibodies eluted from a pool of intravenous immunoglobulin (IVIg) obtained from several thousand healthy donors (pg. 3624, 1st col., 1st PP). The antibodies in the eluate bind to a synthetic RGD sequence-containing peptide AVTGRGDSPA (pg. 3624, 2nd col., last PP). Appellants submit that inhibiting platelet aggregation by a pool of naturally occurring antibodies is not the equivalent to inhibiting $\alpha\text{v}\beta 3$ and/or $\alpha 5\beta 1$ integrin ligand-mediated cell-cell interaction nor the same as inhibiting tumor growth, inflammation and/or angiogenesis in a patient, as recited in Appellants' claims 8 and 15. This is not found to be persuasive because Vassilev *et al* teach that these antibodies are relevant for the immunomodulatory effects of IVIg in autoimmune and inflammatory diseases and for understanding the role of normal IgG in immune homestasis (see page 3624, 2nd col., 2nd full ¶). Vassilev *et al* teach that the RGD motif has a central role in mediating cell-to-cell and cell-matrix adhesion in a variety of immunological and inflammatory processes (see page 3629, bridging ¶). With respect to the antibody, Vassilev *et al* teach that the anti-RGD antibodies bind to AVTGRGDSPA peptide and to proteins expressing the RGD sequence, such as the RGD-containing Fn, vitronectin, fg, and vWF (see pp. 3625, 1st col., under *Binding assays*). Given that the claimed SEQ ID NO: 2 and 41 are RGD-containing peptides, wherein the RGD motif has a

central role in mediating cell-to-cell adhesion, the referenced anti-RGD antibodies would bind to the claimed SEQ ID NO: 2 (EGYIQNYRCRGDDSKVQEAR) and 41 (CRGDD) irrespective of how the antibodies were obtained.

At the bottom of page 11 of the brief, Appellants argue that Vassilev *et al.* do not teach blocking the interaction between VCIP and the $\alpha\beta 3$ and $\alpha 5\beta 1$ integrins. Also, Vassilev *et al.* do not teach VCIP or $\alpha\beta 3$ and/or $\alpha 5\beta 1$ integrins. As stated supra by Appellants, Vassilev *et al.* disclose inhibiting aggregation of platelets. This is not found to be persuasive. Although the reference is silent about blocking the binding of $\alpha\beta 3$ and/or $\alpha 5\beta 1$ integrins to VCIP, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). “{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable”. In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. On this record, it is reasonable to conclude that the same patient is being administered the same active anti-RGD antibodies by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-RGD antibodies to treat inflammation. Vassilev *et al* teach that the RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory process (see page 3629, bridging ¶). The claimed method recites inhibition of “ $\alpha\beta 3$ and/or $\alpha 5\beta 1$ integrin ligand-mediated cell-cell interaction”.

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Vassilev *et al* teachings the inhibition of platelets aggregation (cell-cell) to fibronectin (ligand) is integrin ligand-mediated cell-cell interaction as recited in the preamble of the claim. The integrin being $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ is inherent to the platelets. Platelets do express both $\alpha v\beta 3$ and $\alpha 5\beta 1$ in addition to the $\alpha IIb\beta 3$. That is the anti-RGD antibodies bind to an RGD-containing ligand mediated platelet aggregation (cell-cell interaction) which would lead to the inhibition of the aggregation. The integrin being $\alpha v\beta 3$, $\alpha 5\beta 1$ or $\alpha IIb\beta 3$ is inherent. Both the claimed and the prior art invention are directed to a single method step of inhibiting integrin ligand-mediated cell-cell interaction with anti-RGD antibodies. The prior art anti-RGD antibodies would bind to claimed SEQ ID NOS: 2 and 41, the cell surface integrins including $\alpha v\beta 3$ and $\alpha 5\beta 1$ that recognize the RGD motif would inherently be inhibited in the method. The ligand being VCIP, which is an RGD-containing protein, is inherent in the method which contributes to inflammation. The teaching of record has properly shifted burden to applicant. Attorney argument cannot take the place the evidence lacking in the record. Meitzner v. Mindick, 193 USPQ 17, 22 (CCPA 1977).

On the top of page 12 of the brief, Appellants argue that Vassilev *et al.* do not teach Appellants' SEQ ID NOS: 2 and 41 nor does Vassilev *et al.* teach antibodies specifically directed against these sequences. Also, as stated supra, Vassilev *et al.* do not teach VCIP nor the VCIP sequence of SEQ ID NO: 13. Appellants' antibody is directed against specific peptide sequences of SEQ ID NO: 2 and 14 that are contained within a specific VCIP sequence. Except for the RGD amino acids, Appellants' SEQ ID NOS: 2 and 41 are neither identical nor homologous to the AVTGRGDSPA peptide disclosed in Vassilev *et al.* This is not found to be persuasive. The prior art of Vassilev *et al* need not to teach SEQ ID NOs: 2, 41 or 13 to meet the claimed limitation. Vassilev *et al* teach anti-RGD antibodies that would bind claimed SEQ ID NOs: 2, 13 and 41 because these sequences are RGD containing peptides and proteins. Vassilev *et al* teach that binding of anti-RGD antibodies to the peptide and to proteins expressing the RGD sequence such as the RGD-containing decapeptide, Fn, vitronectin, fg, and vWF (see page 3625, 1st col., under *Binding assays*).

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At the middle of page 12 of the brief, Appellants argue that Vassilev *et al.* teach that the eluted antibodies bind to an RGD-motif containing peptide AVTGRGDSPA, (pg. 3624, 2nd col., last PP). Vassilev *et al.* demonstrate that their antibody eluate can bind to fibronectin, fibrinogen, vitronectin, VWF and laminin in a (pg. 3626, col. 1, 1st full PP). Just because an antibody, such as the antibodies in Vassilev *et al.*, bind to an RGD motif-containing peptide, does not inherently mean the antibodies would necessarily have any inhibitory action upon binding, absent evidence to the contrary. This is not found to be persuasive. Given that the claimed SEQ ID NO: 2 and 41 are RGD-containing peptide sequences, the referenced anti-RGD antibodies would bind to the claimed SEQ ID NO: 2 (EGYIQNYRCRGDDSKVQEAR) and 41 (CRGDD). Moreover, antibodies “cross-react” with antigens with homologous amino acid residues. The reference anti-RGD antibody would bind to the peptide comprises SEQ ID NO: 41 (CRGDD) and 2 (EGYIQNYRCRGDDSKVQEAR) due to the shared sequence homology (RGD motif). Since the office does not have a laboratory to test the reference antibodies, it is Appellant’s burden to show that the reference anti-RGD antibody does not bind to the SEQ ID NO:2 and 41 recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

At the bottom of page 12 of the brief, Appellants contend that the antibodies in Vassilev *et al.* would not bind to the peptide of SEQ ID NO: 2 and 41. In distinct contrast to the Examiner’s assertion, Appellants submit that Appellants’ antibody did not react with other RGD-containing extracellular matrix molecules such as fibronectin, vitronectin, or type I collagen (pg. 40, II, 3-4). The Examiner relies on Bendayan who the Examiner states teaches cross-reactivity of antibodies. Appellants submit that Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin. Bendayan shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and to glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules. Bendayan concludes that an antibody directed against a small peptide sequence, could bind both a specific antigen and molecules **not related** (Appellants emphasis) to the original antigen and could possibly yield a false positive immunocytochemical result (pg. 886, last PP). This is not found to be persuasive because at issue is the prior art anti-RGD antibodies not

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Appellants' antibodies. It is the Examiner's position that the prior art anti-RGD antibodies would bind to the claimed SEQ ID NO: 2 and 41 due to presence of RGD in these sequences. The anti-RGD antibody taught by Vassilev *et al* would bind to the claimed VCIP of SEQ ID NO: 13 and the peptides SEQ ID NOS: 2 and 41 because they all possess the RGD epitope which the anti-RGD antibody would recognize. VCIP possess RGD binding motif similar to those found in native ligands, such as fibronectin, fibrinogen, vitronectin, VWF and laminin, the anti-RGD antibody taught by Vassilev *et al* would bind to the claimed VCIP protein. The shared scaffold is used for the stereochemical presentation of the RGD site for receptor recognition, which makes the RGD epitope accessible to the antibody.

At the middle of page 13 of the brief, Appellants submit that they demonstrate that Appellants' antibody did not crossreact with mouse antigens (pg. 40, II. 5). Appellants submit that the Examiner has not offered any evidence that the antibodies in Vassilev *et al.* will bind an RGD motif in VCIP that results in blocking an interaction with $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins (claim 8) or in inhibiting tumor growth, inflammation and/or angiogenesis in a patient (claim 15). Therefore, Appellants submit that the Examiner is rejecting claims 8 and 15 over Vassilev *et al.* based on only a mere possibility that the antibodies taught therein would produce an inhibitory or blocking effect on VCIP interaction with $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrins. This is not found to be persuasive because at issue is the prior art anti-RGD antibodies not Appellants' antibodies. Appellants fail to show that the reference anti-RGD antibody does not bind to the SEQ ID NO:2 and 41 recited in the claims. Vassilev *et al* teach therapeutic preparations of normal polyspecific IgG (IVIg) containing antibodies that bind to human RGD-containing integrin ligands (see page 3627, under DISSUSSION). Vassilev *et al* teach that the presence of natural IgG antibodies to the RGD motif may contribute to the immunomodulatory and anti-inflammatory effects of therapeutic preparations of normal IgG (see abstract).

At the bottom of page 13 of the brief, Appellants submit that their antibody is specifically directed against all the amino acids in Appellants' peptides of SEQ ID NOS: 2 and 41, and not merely the RGD motif. In partial support for this argument, Appellants previously submitted

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Pedchenko *et al.* who taught that $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins bind both the proximal RGD site and non-RGD motifs within the noncollagenous domain of the alpha3 chain of Type IV collagen. Thus, Pedchenko *et al.* teach that both the RGD and non-RGD motifs contribute to the mechanism of endothelial cell adhesion in the human vasculature. This is not found to be persuasive. The prior art anti-RGD antibodies would bind claimed SEQ ID NO: 2 and 41. There is no requirement that the claimed antibodies bind all the amino acids of SEQ ID NO: 2 and 41. Claim 8 recites “an antibody directed against a peptide consisting of SEQ ID NO: 41 or consisting of SEQ ID NO: 2”, the prior art anti-RGD antibodies would be directed against (bind) a peptide consisting of SEQ ID NO: 41 or 2. Regarding Pedchenko *et al* reference, the examiner notices that both the prior art and the claimed invention are directed the RGD binding site. Moreover, the Examiner found that the claimed ligand for $\alpha v\beta 3$ is VCIP not Type IV collagen as in Pedchenko *et al* reference. Claimed VCIP does not contain non-RGD motifs for $\alpha v\beta 3$.

Rejection of Claims 15 and 32 under 35 U.S.C. §103(a) over U.S. Patent No 5,807,819 in view of U.S. Patent No. 5,567,440 and Vassilev *et al.*, as is evidenced by Bendayan

Appellant's submits on page 15 of the brief that that all the claim elements must be known in the art. Most importantly, Applicants' teach that prior to the instant invention, VCIP was not known to function as an integrin ligand and had no known function other than lipid phosphatase activity (pg. 18, II. 28 to pg. 19, II. 3; Abstract). Thus, as this function of VCIP was unknown at the time of the instant invention, Appellants submit that the a person having ordinary skill in the art, after consideration of U.S. Patent No. 5,807,819 with U.S. Patent No. 5,567,440 and Vassilev *et al.* would not have had a reasonable expectation that Appellant's method of inhibiting tumor growth, inflammation and/or angiogenesis in a patient by administering an antibody directed against a peptide consisting of SEQ ID No. 41 or consisting of SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP) consisting of SEQ ID No. 13 to block the interaction between VCIP and the $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins would be successful. This is not found to be persuasive. It is clear that both the combined prior art and Appellants administer the same antibody to the same patient to achieve

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the same results. The prior art and Appellants have suggested different mechanisms. It is acknowledged that Appellants now recite and believe in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does Appellant provide objective evidence to distinguish the prior art from the claimed invention. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs., 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. Even though Appellant has proposed or claimed the mechanism by which a particular an anti-RGD antibody inhibit tumor growth, inflammation and/or angiogenesis does not appear to distinguish the prior art teaching the same methods to achieve the same end-result.

On page 16 of the brief, Appellants argue that one of ordinary skill in the art could substitute the RGD-motif containing CRGDDVC cyclic peptide taught by U.S. Patent No. 5,807,819 (see SEQ ID NO: 17) with the antibodies that bind the RDG-motif containing peptide AVTGRGDSPA taught by Vassilev *et al.* (as discussed supra) because U.S. Patent 5,567,440 discloses that cell adhesion interactions have a role in human disease and that these interactions can be interrupted by competitive inhibition e.g., with antibodies, soluble ligands which act as a receptor antagonist such as cyclic RGD peptides, soluble receptors or other competitors (col. 1, II. 17- 30). However, simply making this combination cannot render claims 15 and 32 obvious without one of ordinary skill in the art being able to predict that VCIP would function as an integrin ligand. This is not found to be persuasive. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though Appellant has claimed the mechanism by which the anti-RGD antibodies inhibit tumor growth, inflammation and/or angiogenesis does not appear to distinguish the prior art teaching the same or nearly the same methods to achieve the same end result. The prior art teaching of treating the tumor angiogenesis with the same anti-RGD antibodies to achieve the same therapeutic effect does not differ from the claimed methods.

At the bottom of page 16 of the brief, Appellants point to the Examiner states that the claim limitation "blocks the binding of integrins to cell surface VCIP" would be an expected property of the resultant method based on the cited combination. Appellants argue that the Examiner's statement notwithstanding, Appellants submit that one of ordinary skill in the art in making the cited combination could not have predicted with a reasonable expectation of success that the antibodies in Vassilev *et al.* would block the interaction between VCIP and the $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins (claim 15) or inhibit $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ integrin-mediated cell-cell interaction (claim 32) absent the disclosure in Appellants' specification. This is not found to be persuasive because the anti-RGD antibodies would inherently block the binding of $\alpha v\beta 3$ and/or $\alpha 5\beta 1$ to the cell surface VCIP in a patient.

On page 17 of the brief, Appellants submit that a determination of obviousness requires a reasonable expectation of success. The scope of both claims 15 and 32 encompass administering an antibody directed against a peptide consisting of SEQ ID No. 41 or consisting of SEQ ID No. 2 that is derived from a cell surface vascular endothelial growth factor and type I collagen inducible protein (VCIP) consisting of SEQ ID No. 13. The resultant antibody, upon administration to a patient, blocks the interaction between VCIP and the $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins (pg. 35-36, Example 16; Fig. 9). Appellants reiterate that the present invention is the first to disclose that VCIP-derived peptides and proteins act as integrin ligands. As this claim element was unknown, a person having ordinary skill in this art would not have had a reasonable expectation of success based on the cited combination of references. This is not found to be persuasive. There is no evidence that the method of used described in the instant claims would differ in an unexpected manner from those described in the references. In the absence of unexpected results, Appellants' arguments were not found persuasive. The combined reference teachings provide clear motivation and expectation of success in treating angiogenesis with anti-RGD antibodies. One of ordinary skill in the art would have been capable of applying the known methods of substituting an antagonist of RGD-containing peptides for another antagonist (anti-RGD antibodies) to treat angiogenesis and inhibit growth of solid tumors and metastasis. Further, all the claimed elements (inhibiting angiogenesis with RGD antagonist, such as anti-

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RGD antibody) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (targeting RGD) with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating angiogenesis. The claims would have been obvious because a particular known technique (treating angiogenesis with RGD-containing peptides) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (e.g. anti-RGD antibodies) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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